UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/054,638	01/22/2002	Robert P. Ryall	01-059-A	9398

7590 09/04/2008

T. HELEN PAYNE
AVENTIS PASTEUR, INC. INTELLECTUAL PROPERTY
ONE DISCOVERY DRIVE
SWIFTWATER, PA 18370

EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
09/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/054,638	RYALL, ROBERT P.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-46 and 48-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-46 and 48-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicant's Amendment

1) Acknowledgment is made of Applicant's amendment filed 06/12/08 in response to the non-final Office Action mailed 12/12/07.

Status of Claims

2) Claims 18, 22, 29, 33, 35, 48 and 50 have been amended via the amendment filed 12/12/07.

Claims 56 and 57 have been canceled via the amendment filed 12/12/07.

Claims 18-36, 46 and 48-51 are pending and are under examination.

Prior Citation of References

3) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

4) The objection to the specification made in paragraph 5 Office Action mailed 10/03/05 and maintained in paragraph 5 of the Office Action mailed 03/20/07 and in paragraph 6 of the Office Action mailed 12/12/07 under 35 U.S.C. § 132 as introducing new matter, is withdrawn in light of Applicant's amendment to the specification.

Rejection(s) Moot

5) The rejection of claims 56 and 57 made in paragraph 16 of the Office Action mailed 12/12/07 under 35 U.S.C. § 112, first paragraph, as containing new matter, is moot in light of Applicant's cancellation of the claims.

6) The rejection of claims 56 and 57 made in paragraph 19 of the Office Action mailed 12/12/07 under 35 U.S.C. § 103(a) as being unpatentable over Costantino *et al.* (*Vaccine* 10: 691-698, 1992, already of record) as modified by McMaster (US 6,146,902, already of record), Chong *et al.* (WO 99/42130), Lingappa *et al.* (*Vaccine* 19: 4566-4575, August 2001), Perkins BA (*JAMA* 283: 2842-2843, 07 June 2000), Morley *et al.* (*Vaccine*

20: 666-687, 12 December 2001) as applied to claims 33 and 18 above, and further in view of Schneerson *et al.* (US 6,632,437, already of record), is moot in light of Applicant's cancellation of the claims.

Rejection(s) Withdrawn

7) The rejection of claims 18, 19-36, 46 and 48-51 made in paragraph 16 of the Office Action mailed 12/12/07 under 35 U.S.C. § 112, first paragraph, as containing new matter, is withdrawn in light of Applicant's amendment to the base claim.

8) The rejection of claim 22 made in paragraph 17(a) of the Office Action mailed 12/12/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claim.

9) The rejection of claim 35 made in paragraph 17(b) of the Office Action mailed 12/12/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claim.

10) The rejection of claim 48 made in paragraphs 17(c) and 17(d) of the Office Action mailed 12/12/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claim.

11) The rejection of claims 23-25, 36, 49 and 50 made in paragraph 17(e) of the Office Action mailed 12/12/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the base claim.

12) The rejection of claims 18-36, 46 and 48-51 made in paragraph 18 of the Office Action mailed 12/12/07 under 35 U.S.C. § 103(a) as being unpatentable over Costantino *et al.* (*Vaccine* 10: 691-698, 1992, already of record) in view of McMaster (US 6,146,902, already of record), Chong *et al.* (WO 99/42130, already of record), Lingappa *et al.* (*Vaccine* 19: 4566-4575, August 2001), Perkins BA (*JAMA* 283: 2842-2843, 07 June 2000), Morley *et al.* (*Vaccine* 20: 666-687, 12 December 2001), is withdrawn in light of Applicant's amendment to the claims and/or the base claim. Applicant's arguments with regard to this rejection have been considered, but are moot in light of the withdrawal of the rejection.

Rejection(s) Maintained

13) The provisional rejection of claims 18-33 made in paragraph 15 of the Office Action mailed 12/12/07 under the judicially created doctrine of obviousness-type double patenting over claim 56 of the co-pending application 11232160 is maintained for the reasons set forth therein. Applicant requests that the rejection be held in abeyance until allowable subject matter is indicated in either application.

Response to Applicant's Arguments on Obviousness Rejection(s)

14) Applicant submits the following arguments. Applicant's arguments have been carefully considered, but are not persuasive.

(a) The Office failed to address the objective evidence presented in the last paper in the form of third party references and supporting remarks. See last full paragraph of Applicant's amendment/response filed 6/12/08. Yet, at the bottom of page 14 of his amendment/response filed 6/12/08, Applicant readily acknowledges that the Office sought to rebut the Gizurarson paper. The arguments of Applicant were addressed to the extent relevant to the art rejections then pending. The alleged lack of success and the unpredictability of combining several components in a vaccine were addressed. In particular, the prior art reference of Tai *et al.* was cited, which demonstrated, with particular reference to a combined multivalent meningococcal glycoconjugate vaccine, the predictable efficacy and success. As readily acknowledged by Applicant at bottom paragraph of page 14 of his response filed 06/12/08, the Office Action mailed 03/19/07 did address the alleged unpredictability taught by Gizurarson and showed that Gizurarson's teachings are not pertinent to a combination meningococcal glycoconjugate vaccines, the subject matter of the instant application. Applicant even reproduces a part of the Office's rebuttal with regard to Gizurarson at the top of page 15 his amendment/response filed 06/12/08, which is evidence that the Office did address the objective evidence presented.

(b) Chong *et al.* has not previously been used in any obviousness rejection. Applicant objects to raising Chong *et al.* at this point of prosecution. The reference of Chong *et al.* is currently not applied in view of the anticipatory reference of Beuvery *et al.* (*Infect. Immun.* 41: 609-617, 1983), which taught in 1983 a tetravalent conjugate vaccine comprising four conjugates of purified capsular polysaccharides of four different

meningococcal serogroups, A, C, W-135 and Z, wherein each of the purified capsular polysaccharide is individually conjugated to the protein carrier, tetanus toxoid. See the art rejection(s) set forth below. It is particularly noted that several years into prosecution Applicant has *failed* to disclose the reference of Beuvery *et al.* to the Office as required under § 1.56. Furthermore, nothing in MPEP prohibits the Office from using any relevant prior art reference including Chong *et al.* as is appropriate under § 102 or § 103 to reject claims as they get amended.

(c) All four *Graham* factors must be considered in determining obviousness under § 103 and each piece of the Applicant's evidence of non-obviousness must be weighed. The *Graham* decision emphasized that the TSM is one important component of obviousness examination. The *KSR* decision did not strike down the well settled teaching, suggestion and motivation to combine (TSM) test promulgated by the Federal Circuit. According to MPEP § 2143: (i) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (ii) there must be a reasonable expectation of success and (iii) the prior art reference, or references when combined, must teach or suggest all the claim limitations.

(d) The *KSR* decision was based on the facts arising from a simple and predictable mechanical art. The scope and content of the prior art at issue involved the combination of known components functioning their usual and customary ways. The U.S. Supreme Court did not pass its *KSR* decision in an unpredictable filed where function known elements sometimes cannot be predicted. Even when combining known elements, the Supreme Court cautioned that a patent composed of several elements is not proved obvious merely by demonstrating that each of the elements was, independently, known in the prior art (*KSR*, page 14). The focus of *KSR* can be summarized by saying common sense dictates that the predictability, and conversely the unpredictability, in a given field of inventive endeavor must be weighed in every obviousness determination. *Graham* explicitly cautions that standards are needed during examination to guard against slipping into use of hindsight, and to resist the temptation to read into the prior art the teachings of the invention in issue. The prohibition against the use of hindsight during

obviousness examination is alive and well. The *KSR* decision did not 'green-light' the use of hindsight during obviousness examination. The rigid TSM analysis rejected in *KSR* is currently being employed in the instant case because the Office has disregarded the totality of evidence pertaining to the *Graham* factors.

(e) Applicant's arguments on the alleged unpredictability teaching by Lindberg or Butterfly *et al*. and the alleged lack of likelihood of technical success by Perkins have been fully considered. However, the express demonstration by Beuvery *et al*. (*Infect. Immun*. 41: 609-617, 1983) of the predictable and successful immunogenicity of a tetravalent conjugate vaccine comprising four conjugates of purified capsular polysaccharides of four different meningococcal serogroups, A, C, W-135 and Z, wherein each of the purified capsular polysaccharide was individually conjugated to the protein carrier, tetanus toxoid, indicates against the alleged unpredictability. See the art rejection(s) set forth below. Furthermore, Butterfly's alleged teaching of unpredictability is not relevant to the instantly claimed invention since the instant claims do not combine a monovalent serogroup C meningococcal conjugate vaccine with a heterologous, Gram positive, non-meningococcal '9-valent pneumococcal conjugate vaccine'. Moreover, Beuvery *et al*. in addition to demonstrating successful immunogenicity, reported no antigenic (intermolecular) competition in the response to group C polysaccharide and tetanus toxoid, after injection of a mixture of four distinct, individually made polysaccharide-tetanus toxoid conjugates, including the group C polysaccharide conjugate.

The factors such as predictability or unpredictability and expectation of success must be evaluated within the art of multivalent meningococcal capsular polysaccharide conjugate vaccines as opposed to staphylococcal capsular polysaccharide conjugate vaccines. Therefore, NABI's alleged failure with a staphylococcal capsular polysaccharide conjugate vaccine is irrelevant to the obviousness rejection set forth in the instant application. What are directly relevant to the issue however are the teachings of Beuvery *et al*. (*Infect. Immun*. 41: 609-617, 1983 - see seventh full paragraph on page 615); Tai *et al*. (*Abstracts of the Tenth International Pathogenic Neisseria Conference*, (Ed) Zollinger *et al*. September 8-13, Baltimore, USA, pages 214-215, 1996 – see

paragraph 20 of the Office Action mailed 12/12/07); and Fusco *et al.* (*Expert Opin. Investig. Drugs* 7: 245-252, 1998 – see under section 'Relevant Prior Art' below), which clearly demonstrated the lack of unpredictability and a showing of complete success with regard to the immunogenicity of the multivalent meningococcal capsular polysaccharide-protein conjugate vaccines. Particularly noteworthy is Beuvery's showing in 1983. After injection of a mixture of four distinct, individually made polysaccharide-tetanus toxoid conjugates, including the group C polysaccharide conjugate, Beuvery *et al.* reported no antigenic (intermolecular) competition in the response to group C polysaccharide and tetanus toxoid, even though the same carrier protein was used. Tai *et al.* established reasonable expectation of success of combining multiple different meningococcal serogroup capsular polysaccharide-protein conjugates, including even the poorly immunogenic serogroup B meningococcal capsular polysaccharide, in producing an immunogenic combination conjugate vaccine and reported no unpredictability and no indication of carrier-induced epitopic suppression associated with such a combination vaccine. Similarly, Fusco *et al.* already established reasonable expectation of success of combining three different meningococcal serogroup capsular polysaccharide-protein conjugates including the poorly immunogenic serogroup B capsular polysaccharide to produce an immunogenic combination conjugate vaccine that generated *CPS-specific bactericidal antibodies to each of the three major serogroups of meningococci*. Fusco's studies too indicate total lack of unpredictability and lack of carrier-induced epitopic suppression associated with such a combination vaccine.

Applicant's arguments on the teachings of Levine *et al.* and Applicant-submitted papers of Bishai *et al.* on AIDS vaccine and Scott *et al.* are moot in light of the new rejection(s) based on the hitherto undisclosed reference of Beuvery *et al.* In the instant case, contrary to Applicant's assertion, all four *Graham* factors have been considered in determining obviousness under § 103 and the TSM test has been evaluated. As per MPEP § 2143, suggestion or motivation to combine the teachings of Beuvery *et al.* and McMaster has been established via Perkins' teachings and as it existed in the knowledge generally available to one of ordinary skill in the art; the reasonable expectation of success as taught by Beuvery *et al.* has been established; and the prior art references

when combined, do teach or suggest all the claim limitations. The objective evidence of non-obviousness cannot overcome a strong *prima facie* case of obviousness. In the 'textbook case' for obviousness, *Agrizap, Inc. v. Woodstream Corp.*, 520 F.3d 1337, 86 USPQ 2d 1110 (Fed. Cir. 2007) involving predictable art, it was held that objective evidence of non-obviousness such as commercial success, long-felt need in the market, and copying by others cannot overcome a strong *prima facie* case of obviousness. In the instant case, the combining of the art-known McMaster's serogroup Y capsular polysaccharide-protein conjugate to the already existing Beuvery's immunogenic multivalent meningococcal serogroups A, C and W-135-containing conjugate composition, would have resulted in an immunogenic multivalent, broadest approach-based, stand-alone combination meningococcal capsular polysaccharide conjugate composition of serogroups A, C, Y and W-135 that addresses the variation in serogroup distribution by region and age and the potential for capsular switching, as taught by Perkins. See the art rejections below.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

15) Claim 18 and the dependent claims 19-36, 46 and 48-51 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 18, as amended, includes the new limitations: 'purified', 'human' and 'at least' one of said polysaccharides. The amended claim 18 is now drawn to an immunological composition comprising a combination of two, three, or four distinct and separately made 'purified' protein-capsular polysaccharide conjugates, wherein each of the conjugates comprises a purified capsular polysaccharide from *N. meningitidis,* wherein each of the conjugates comprises a purified capsular polysaccharide from *N. meningitidis* of serogroup A, C, W-135 or Y conjugated to a carrier protein, wherein at least one serogroup is W-135 or Y, further wherein said immunological composition is capable of eliciting an immune response in a human to 'at least' one of said polysaccharides. Applicant states that paragraphs 0017-0021, 0036, 0037 and 0078 to 0091 of the

specification provide support for the amendments. However, these parts of the instant specification, as filed, are not supportive of an immunological composition as claimed in the amended claim 18 which encompasses an immunological composition that is required to comprise a combination of 2, 3, or 4 separately made purified protein-capsular polysaccharide conjugates of serogroup A, C, W-135 and Y wherein at least one serogroup is required to be W-135 or Y, and wherein the composition is required to have the capacity to elicit an immune response in a mammal selectively to only one, only two, or only three of said capsular polysaccharides. However, such a bivalent, trivalent or tetravalent conjugate having the unique capacity to elicit an immune response selectively to only one of the two, three or four recited serogroup capsular polysaccharides, only two of the three or four recited serogroup capsular polysaccharides, or only three of the four recited serogroup capsular polysaccharides, but not to the rest of the recited serogroup capsular polysaccharides. Therefore, the above-identified new limitations in claim 18 are considered to be new matter. New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P. 608.04 to 608.04(c).

Applicant is invited to point to specific line and page numbers of the specification, as originally filed, that provide descriptive support for the limitations identified above, or alternatively to remove the new matter from the claim(s). Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06.

Rejection(s) under 35 U.S.C. § 102

16) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17) Claims 18-22, 24-29, 31 and 32 are rejected under 35 U.S.C. § 102(b) as being anticipated by Beuvery *et al.* (*Infect. Immun.* 41: 609-617, 1983).

The transitional limitation 'comprising', which is synonymous with 'including', 'containing', or 'characterized by', is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; and *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ('comprising' leaves 'the claim open for the inclusion of unspecified ingredients even in major amounts').

Beuvery *et al.* taught a vaccine composition comprising a mixture of individually made conjugates of purified capsular polysaccharides of four different meningococcal serogroups, A, C, W-135 and Z, wherein each of the purified capsular polysaccharide is individually conjugated to the protein carrier, tetanus toxoid. The prior art liquid composition was used to immunize mice, wherein the composition elicited an immune response to at least one of the capsular polysaccharides. See paragraph bridging pages 613 and 614; 'Materials and Methods'; Table 5; and seventh full paragraph on page 615. The prior art composition that elicited an immune response in mice to at least one of the capsular polysaccharides is expected to necessarily have the inherent capacity of eliciting an immune response in a human to at least one of the capsular polysaccharides.

Claims 18-22, 24-29, 31 and 32 are anticipated by Beuvery *et al.*

Rejection(s) under 35 U.S.C. § 103

18) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or unobviousness.

19) Claims 34-36, 46 and 48 are rejected under 35 U.S.C § 103(a) as being unpatentable over Beuvery *et al.* (*Infect. Immun.* 41: 609-617, 1983) as applied to claim 18 above, and further in view of Fusco *et al.* (*Expert Opin. Investig. Drugs* 7: 245-252, 1998).

The teachings of Beuvery *et al.* are explained above, which do not expressly teach the presence of an adjuvant such as aluminum hydroxide in their vaccine composition comprising the mixture of the conjugates wherein the purified capsular polysaccharides of four different meningococcal serogroups, A, C, W-135 and Z, are conjugated to the single carrier protein species, tetanus toxoid.

However, adding an art-known, conventional adjuvant such as aluminum hydroxide, to an art-disclosed vaccine composition was well known and routinely practiced in the art at the time of the invention. For instance, Fusco *et al.* taught of the routine and conventional use of aluminum hydroxide adjuvant in a multivalent meningococcal capsular polysaccharide-protein conjugate vaccine. See the Figure 4 legend for example.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add Fusco's aluminum hydroxide adjuvant to Beuvery's vaccine composition comprising a mixture of conjugates of purified capsular polysaccharides of four different meningococcal serogroups, A, C, W-135 and Z to produce the composition of the instant invention with a reasonable expectation of success. Given that it is routine and conventional in the art to add aluminum hydroxide adjuvant to a multivalent meningococcal conjugate vaccine as shown by Fusco *et al.*, one of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of enhancing the immune response to Beuvery's conjugate vaccine composition.

Claims 34-36, 46 and 48 are *prima facie* obvious over the prior art of record.

20) Claim 33 is rejected under 35 U.S.C § 103(a) as being unpatentable over Beuvery *et al.* (*Infect. Immun.* 41: 609-617, 1983) as applied to claim 18 above, and McMaster

(US 6,146,902, already of record) and further in view of Perkins BA (*JAMA* 283: 2842-2843, 07 June 2000, already of record).

The teachings of Beuvery *et al.* are explained above, which do not expressly teach that their combined conjugate vaccine composition comprises a purified capsular polysaccharide-carrier protein conjugate of serogroup Y *N. meningitidis.*

However, individually produced meningococcal serogroup Y capsular polysaccharide-protein conjugate vaccine was already known in the art at the time of the instant invention. For example, McMaster disclosed individually made purified meningococcal Y capsular polysaccharide-protein carrier conjugate vaccine and provided detailed teachings as to how to successfully make the individual purified meningococcal Y capsular polysaccharide-protein carrier conjugates in addition to making purified meningococcal A, C and W-135 capsular polysaccharide-protein carrier conjugates. McMaster disclosed a vaccine or immunological composition comprising a sterile liquid solution of individual capsular polysaccharide-protein conjugates comprising purified capsular polysaccharides of *Neisseria meningitidis* belonging to the serogroup A, C, W-135 and Y conjugated to diphtheria toxoid protein for human or animal use. Column 7; Table 3; lines 59-64 of column 3; paragraph bridging columns 3 and 4; and lines 3-6 in column 4. The serogroup Y meningococcal capsular polysaccharide conjugate is identified by the lot number D01880. See Table 3. The production of meningococcal serogroup A, C, Y and W-135 conjugates are described in columns 6 and 7; and Example 1.

Perkins expressly included meningococcal serogroups A, C, Y and W-135 in the list of globally most important causes of meningococcal disease. See third full paragraph on page 2842. Perkins taught that because of the variation in serogroup distribution by region and age and potential for capsular switching, there is an identified need for development and availability of *multivalent* meningococcal conjugates, with all of meningococcal serogroups A, C, Y and W-135, as stand-alone vaccines and in combination with other vaccines. Perkins expressly suggested the inclusion of A, C, Y and W-135 serogroups in conjugate meningococcal vaccines as the broadest approach

based on the current understanding of *N. meningitidis*. See last two full paragraphs on page 2843.

With the concept of providing multiple meningococcal serogroup capsular polysaccharide-protein conjugates in a multivalent immunogenic formulation already known in the art as demonstrated by Beuvery *et al.*, and given that individually produced purified meningococcal serogroup Y capsular polysaccharide-protein conjugate was already known in the art as taught by McMaster, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine McMaster's individually produced, sterile, purified meningococcal serogroup Y capsular polysaccharide-protein conjugates with Beuvery's vaccine composition comprising a mixture of conjugates of purified capsular polysaccharides of four different meningococcal serogroups, A, C, W-135 and Z to produce the composition of the instant invention. With the identified need in the art for development and availability of *multivalent* meningococcal conjugates with all of meningococcal serogroups A, C, Y and W-135 as stand-alone vaccines and in combination with other available vaccines as expressly taught by Perkins, and with the reasonable expectation of success already demonstrated in the art with a tetravalent meningococcal conjugate vaccine by Beuvery *et al.*, one of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of providing a multivalent, broadest approach-based, stand-alone combination meningococcal capsular polysaccharide conjugate composition of serogroups A, C, Y and W-135 that addresses the variation in serogroup distribution by region and age and the potential for capsular switching, as taught by Perkins.

Claim 33 is *prima facie* obvious over the prior art of record.

21) Claim 51 is rejected under 35 U.S.C § 103(a) as being unpatentable over Beuvery *et al.* (*Infect. Immun.* 41: 609-617, 1983) as applied to claims 33 and 18 above, and further in view of McMaster (US 6,146,902, already of record).

The teachings of Beuvery *et al.* are explained above, which do not expressly teach that their liquid conjugate composition comprising the mixture of meningococcal conjugates is formulated as a sterile liquid.

However, the production of meningococcal conjugate vaccines in a sterile liquid form was routine and conventional in the art at the time of the invention. For instance, McMaster taught a method of rendering purified capsular polysaccharide-protein conjugates of multiple serogroups via sterile filtration using a membrane filter. See second full paragraph in column 5.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to render Beuvery's individual purified meningococcal serogroup conjugates prior to mixing them into a combined conjugate composition using McMaster's sterile membrane filtration to produce the instant invention. One of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of rendering Beuvery's multivalent liquid conjugate composition free of contaminants since it is routine in the art to provide a vaccine in a sterile form.

Claim 51 is *prima facie* obvious over the prior art of record.

22) Claims 49 and 50 are rejected under 35 U.S.C § 103(a) as being unpatentable over Beuvery *et al*. (*Infect. Immun*. 41: 609-617, 1983) as modified by Fusco *et al*. (*Expert Opin. Investig. Drugs* 7: 245-252, 1998) as applied to claim 48 above, and further in view of Costantino *et al*. (*Vaccine* 10: 691-698, 1992, already of record).

The teachings of Beuvery *et al*. as modified by Fusco *et al*. are explained above, which do not teach the carrier protein species in the conjugate to be diphtheria toxoid or CRM197.

However, the use of CRM197 diphtheria toxoid as an alternate carrier protein in a meningococcal capsular polysaccharide conjugate vaccine was routine and conventional in the art at the time of the invention. For instance, Costantino *et al*. taught the use of CRM197 carrier protein to produce a multivalent meningococcal conjugate vaccine composition by individually conjugating CRM197 to a purified meningococcal serogroup A capsular polysaccharide conjugated and a purified meningococcal serogroup C capsular polysaccharide, wherein the vaccine composition induced a significant increase in antibodies to group A and C meningococcal capsular polysaccharides. See abstract; Materials and Methods; Results; Figures 5 and 6; and Table 2.

Given the routine and conventional use of CRM197 carrier protein in the production of a conjugate vaccine composition comprising individually produced purified meningococcal capsular polysaccharide conjugates as taught by Costantino *et al.*, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use an alternative, already art-known carrier protein such as Costantino's CRM197 carrier protein in place of tetanus toxoid in Beuvery's meningococcal conjugates to produce the instant invention. Substitution of one art-known carrier protein with another, alternative, functionally equivalent carrier protein such as CRM197 for the same purpose of serving as a carrier protein in the conjugates would have been well within the realm of routine experimentation, would have been obvious to one of ordinary skill in the art, and would have brought about similar predictable results or effects.

Claims 49 and 50 are *prima facie* obvious over the prior art of record.

Relevant Prior Art

23) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicant's disclosure:

- Fusco *et al.* (*Expert Opin. Investig. Drugs* 7: 245-252, 1998) taught a trivalent combination vaccine comprising individual meningococcal serogroup A, B and C conjugates. The trivalent conjugate vaccine was shown to be safe and highly immunogenic in mice and non-human primates, *generating CPS-specific bactericidal antibodies to each of the three major serogroups of meningococci*. Fusco *et al.* taught that this trivalent conjugate vaccine would be expected to provide world-wide protection against meningococcal disease. See abstract. Thus, the concept of combining two or more individually produced meningococcal capsular polysaccharide-protein conjugates in a multivalent conjugate formulation that elicited bactericidal antibodies to each of the serogroup capsular polysaccharides including the serogroup B capsular polysaccharide in mice and non-human primates was already known in the art. Fusco *et al.* already established reasonable expectation of success of combining three different meningococcal serogroup capsular polysaccharide-protein conjugates including the poorly immunogenic serogroup B capsular polysaccharide to produce an immunogenic combination conjugate vaccine that generated *CPS-specific bactericidal antibodies to each of the three major*

serogroups of meningococci. Fusco's studies indicate total lack of unpredictability and lack of carrier-induced epitopic suppression associated with such a combination vaccine. See entire document.

Remarks

24) Claims 18-36, 46 and 48-51 stand rejected.

25) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. The Fax number for submission of amendments, responses and/or papers is (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

26) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

27) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Shanon Foley, can be reached at (571) 272-0898, or Robert Mondesi, can be reached at (571) 272-0956.

/S. Devi/
S. Devi, Ph.D.
Primary Examiner
AU 1645